
Selecting for neurogenic potential as an alternative for Alzheimer's disease drug discovery.

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Authors:	Marguerite Prior, Joshua Goldberg, Chandramouli Chiruta, Catherine Farrokhi, Mariya Kopynets, Amanda J Roberts, David Schubert
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Public Summary:

INTRODUCTION: Neurons die in Alzheimer's disease (AD) and are not effectively replaced. An alternative approach to maintain nerve cell number is to identify compounds that stimulate the proliferation of endogenous neural stem cells in old individuals to replace lost neurons. However, unless a neurogenic drug is also neuroprotective, the replacement of lost neurons will not be sufficient to stop disease progression. METHODS: The neuroprotective AD drug candidate J147 is shown to enhance memory, improve dendritic structure, and stimulate cell division in germinal regions of the brains of very old mice. Based on the potential neurogenic potential of J147, a neuronal stem cell screening assay was developed to optimize derivatives of J147 for human neurogenesis. RESULTS: The best derivative of J147, CAD-031, maintains the neuroprotective and memory enhancing properties of J147, yet is more active in the human neural stem cell assays. DISCUSSION: The combined properties of neuroprotection, neurogenesis, and memory enhancement in a single drug are more likely to be effective for the treatment of age-associated neurodegenerative disorders than any individual activity alone.

Scientific Abstract:

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